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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STANDLEY, STEVEN H	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/777,883	CHERVONSKY ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *3,7,8 and 10-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9, and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed 1/11/06 has been made of record. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Objections/Rejections: Withdrawn

Oath/Declaration

2. Objection to the Oath/declaration for un-initialed and dated changes is withdrawn due to applicant's argument.

Claim Objections

3. Objection to claims 1-6 and 9 for using undefined acronyms is withdrawn due to applicant's amendment/argument.

Claim Rejections - 35 USC § 112

4. Rejection of claim 4 under 35 USC § 112, 1st paragraph, enablement is withdrawn due to applicant's amendment limiting the claim from 'modulates' to 'inhibits' expression.

Claim Rejections - 35 USC § 102

5. Rejection of claims 1-3, 5-6, and 9 under 35 USC § 102(a) over Sasaki et al is withdrawn due to applicant's argument.

6. Rejection of claims 1-3 under 35 USC § 102(b) over Hermida et al is withdrawn due to applicant's amendment.

7. Rejection of claims 1-3 and 5-6 under 35 USC § 102(b) over Engenman is withdrawn due to applicant's amendment.

Objections/Rejections: Maintained/New Grounds

Claim Rejections - 35 USC § 112

8. Rejection of claims 1-3, 5-6, and 9 under 35 USC § 112, 1st paragraph, enablement is maintained for the reasons made of record in the office action dated 9/07/05. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the amendments to the claims as amended render the rejection moot and that otherwise the specification provides ample guidance for the claimed invention. Applicant states on page 8 of Remarks that "The specification describes that "antagonists of CCL21 include compounds (agents) which reduce or inhibit functions of CCL21....For example, agonists or antagonists of CCL1 can be an antibody against CCL21, a mutated or mimic form of CCL21, or a peptidomimetic."

This is not found persuasive because the specification does not teach one skilled in the art how to make a generic 'antagonist' of CCL21. One can undoubtedly look for an antagonist, and perhaps find one, but applicant is claiming a genus that would

require undue experimentation. As indicated in the prior office action, there are a few examples of N-terminal truncations of CCL21, pertussis toxin, and an anti-CCL21 antibody known to inhibit the interaction, the activity, or the function of CCL21/CCR7 interactions. The antibody works by binding to CCL21 and inhibiting its interaction with CCR7. Pertussis toxin works by inhibiting G-protein coupling to receptors such as CCR7. The N-terminal truncations of CCL21 presumably work by binding to CCR7 but not activation it. These polypeptides are not structurally related and do not function in the same way to inhibit CCL21 signaling through CCR7. Thus, they provide no evidence of possession of a structurally and functionally defined genus of 'antagonists' that are claimed. In short, the claims encompass compounds that neither the specification nor the art has defined structurally or functionally, and that one of skill in the art could not envision.

9. Rejection of claim 4 under 35 USC § 112, 1st paragraph, enablement is maintained for the reasons made of record in the office action dated 9/07/05. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the amendments to the claims as amended render the rejection moot and that otherwise the specification provides ample guidance for the claimed invention. Applicant also argues that the specification teaches antisense therapy and that antisense therapy is routine in the art.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 4 is a method of modulating homing of T-cells to the pancreas by contacting the cells with an agonist or antagonist of the chemokine CCL21, wherein the agonist or antagonist modulates CCL21 expression. This is a complex biological process involving many receptors, secreted factors, and cell types. Further the art teaches that antisense nucleic acid therapy is highly unpredictable. For instance the " "Report and Recommendations of the Panel to Assess the NIH Investment n Reseach on Gene Therapy" states that:

"While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of morte than 100 recombinant DNA Advisory Committee (RAC)-approved protocols.

Significant problems remain in all basis aspects of gene therapy. Major difficulties at the basic level include "shortcomings in all current gene transfer vectors

and inadequate standing of the biological interaction of these vectors with the host [page 1]."

The prior art provides for no compound or drug that modulates (i.e., agonizes or antagonizes) *expression* of CCL21, nor does it suggest its usefulness in modulating of the homing of T-cells, and the effect any new compound would have on CCL21 expression is highly unpredictable. Furthermore, no successful gene therapy of any kind has been provided for the instant treatment.

The specification provides no agonist or antagonist that modulates the expression of CCL21, nor does it provide any evidence by way of examples or guidance for the making or usefulness of modulating CCL21 expression in the modulating of T-cell homing to the pancreas. Further, the specification does not teach or show by way of example gene therapy for the method claimed.

The breadth of the claims are such that one skilled in the art would not know how to make or use an agonist or antagonist of CCL21 for modulating T-cell homing to the pancreas. No structural limitations are recited, and the functional limitation includes both inhibition and enhancement.

Thus, given the nature of the invention, the state of the prior art, the lack of any guidance by way of working examples or disclosure in the specification and the breadth of the claims, one skilled in the art would not know how to make or use the invention of claim 4.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Rejection of claims 1-6 and 9 under 35 USC § 112, 1st paragraph, written description is maintained for the reasons made of record in the office action dated 9/17/05. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the claimed subject matter is sufficiently described in the specification and indicates that, for instance, page 14, line 14 provides support for the subject matter as claimed. Further, Applicant argues that "information which is well-known in the art need not be described in detail in the specification." However, the support in the specification is limited to mere functional recitations with no specific structural limitations. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for obtaining it. The compound itself is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3, and 5-6 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Gladue et al (US pgpub # 2002/0168358 A1; published November 2002, filed March 2002, with priority to provisional 60/287, 511 filed April 30, 2001).

Gladue et al teach compounds for administration (section 00159) that are antagonists of SLC/CCR7 interaction (section 0019) for the treatment of autoimmune diseases that include Type I diabetes (section 0039). These compounds will inherently inhibit CD8+ T-cells that are specific for an islet antigen which is insulin from homing to islets of langerhands. Therefore Gladue et al. meets the limitations of claims 1-3, and 5-6.

12. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamoto et al (1980).

Okamoto et al teach administration of islet interacting protein (IAP) to mice with hereditary diabetes as effective treatment of diabetes. IAP is also known as Pertussis Toxin (see Sigma product information below). As described earlier, Sasaki et al of the prior office action demonstrate that Pertussis Toxin antagonizes the CCR7 receptor. Thus, administration of IAP inherently inhibits CD8+ T-cells that are specific for an islet antigen from homing to islets of Langerhands. Therefore Okamoto et al meets the limitations of claims 1-3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gladue et al in further view of Sasaki et al (Jan, 2003).

Gladue et al teaches as described above in the rejection under 35 USC 102 (e). Gladue et al teaches antagonists of the CCL21/CCR7 interaction are useful for the treatment of type I diabetes.

Gladue et al does not teach N-terminal truncations of CCL21 are antagonists of the CCR7 receptor.

Sasaki et al teach that N-terminal truncations of CCL21 are antagonists of the CCR7 receptor (see abstract).

One of ordinary skill in the art would be motivated to combine the teachings of Gladue et al. with those of Sasaki et al. because Gladue et al teaches that the truncations of Sasaki et al would be useful for treatment of type-I diabetes.

14. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gladue et al in further view of Yoon et al. (1999).

Gladue et al teaches as described above in the rejection under 35 USC 102 (e). Gladue et al teaches antagonists of the CCL21/CCR7 interaction are useful for the treatment of type I diabetes. Gladue further teach that the CCL21/CCR7 interaction causes the migration of T-cells and dendritic cells into zones wherein antigen presentation to the T-cells occurs (section 0015), which mediates autoimmune diseases such as diabetes type I. Gladue et al state that "As aforementioned, autoimmune disease, transplant rejection, allergy, and inflammation represent disease states wherein undesired activation of antigen-specific T-cells appears necessary for induction and/or progression of the unwanted clinical state. Accordingly, pharmaceutical compounds that interrupt activation of T-cells [such as antisense knockdown of CCL21], or specific downstream signaling events, are expected to be of great therapeutic value [section 0010]." Further, Gladue teaches compounds that inhibit expression of the CCR7 receptor to treat autoimmune diseases such as diabetes type I.

Gladue et al do not teach inhibiting expression of CCL21 via nucleic acids. Nomiyama et al teach that a knockout of CCL21 (AKA SLC) causes inhibition of T-Cell and dendritic cell migration (page 1272). In other words, inhibition of expression of

CCL21 via modification of nucleic acids inhibits the same process taught by Gladue et al.

Nomiyama et al do not teach administration of an antisense transgene to inhibit the expression of a polypeptide that stimulates autoimmunity.

Yoon et al (1999) teach suppression of autoimmunity through expression of an antisense transgene of GAD in pancreatic islet cells to inhibit the generation of diabetogenic T-cells (see abstract).

One of ordinary skill in the art would be motivated to combine the teachings of Gladue et al with Nomiyama et al and Yoon et al because Gladue et al states that "Accordingly, pharmaceutical compounds that interrupt activation of T-cells [such as antisense knockdown of CCL21], or specific downstream signaling events, are expected to be of great therapeutic value." And Yoon et al demonstrates that the effect of both Nomiyama et al and Gladue et al can be accomplished by administering a transgene an animal.

One would have a reasonable expectation of success because Nomyama et al already demonstrated that the CCL21 knockout had the effect of inhibiting the CCL21/CCR7 interaction taught by Gladue et al, whom also teaches inhibiting CCL21/CCR7 for treatment of type I diabetes.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The Sigma product information on Pertussis Toxin indicates that the toxin is also known by the name "islet activating protein (IAP)." See synonyms.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Steven Standley, Ph.D.
3/27/06

LORRAINE SPECTOR
PRIMARY EXAMINER